Peer Review File

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Reviewer Comments

Reviewer A

Comment 1: "ADAMTS13 cleaves endothelium-derived ultra large VWF" appears in several places. It may not be an accurate statement as ADAMTS13 can cleave platelet-derived ULVWF, although endothelium-derived ULVWF is critical for thrombotic diseases such as TTP.

Reply 1: We agree that ADAMTS13 can cleave platelet derived ULVWF, which may be a small component of VWF pool in circulation. However, cleavage of endothelial ULVWF is the most important function of ADAMTS13, relevant to thrombosis.

Comment 2: The reference is missing for the "Jin et al. (2013)" publication cited in lines 109 – 116.

Reply 2: The reference Jin et al. is now added as ref. 45 in the revised manuscript.

Reviewer B

Comment 1: Since the Prospective focuses on the CRISPR/Cas genetic modifications, it would be very nice to briefly describe the genetic approaches in pre-clinical models to either recreate a loss of function or a point mutation, and how those approaches are important to phenocopy a human disease. This paragraph could also be supported by a chronologic addition to figure one, where the genetic approach is highlighted on each model, indicating whether loss of function or point mutation is achieved, and including in Figure 1, the PROSPECT or future: - point mutations causative of disease or associated with development of iTTP.

Reply 1: We appreciate the comments. However, all animal models established are loss function mutations either using classic ESC or CRISPR/cas approach. No one has made point mutation on ADAMTS13 to create congenital TTP. It is not known whether a point mutation on ADAMTS13 results in autoantibody formation. Thus, it is very difficult to predict how it will work.

Comment 2: In LINE 108: Explain what is AAV- the adenovirus-based gene therapy, etc.? In Line 177: explain the FRETS assay briefly...

Reply 2: We have spelled out the AAV and FRETS, which are the adeno associated virus and fluorescent resonance energy transfers, respectively.

Comment 3: Figure 1: Danio rerio (not Denio rerio, please verify all scientific species names).

Reply 3: This has been corrected.

Comment 4: Line 74: introduction OF the genetic...

Line 81: development of AN acute...

Line 90: While THE A subunit.

Line 97: ADAMTS13 KO mice WHICH received... Line 100: Despite THE transient...

Line 132: and VWF in THE pathogenesis... Line 144: to incite AN acute...

Line 148: reported THE first...

Line 158: their PLASMA ADAMTS13...

Line 161: mechanisms PRESENT in baboonS THAT confer... Line 194: WHEN an intravenous...
Line 195: ACTIVITY
Line 198: and kidneys in THE DECEASED MICE... (but could be written differently as well...)
Reply 4: All typos or misuse of English words have been revised and corrected.

Reviewer C

Comment 1: Provide more information regarding the mechanisms of thrombocytopenia; how do the platelets are cleared after they interact with A1 domain (and/or RGD motif) on ultra large VWF? Why do the thrombi are "widespread VWF-rich but fibrin-poor hyaline"? Is this due to the high shear stress so that red blood cells, leukocytes cannot be trapped into the VWF net? Are these platelets on ultra large VWF activated and PS positive? If so, why cannot they provide negative charge surface for thrombin and fibrin formation? These can be further discussed for the growing readership of AOB.

Reply 1: These are great questions for which we don't have the answers. What we have is speculation, which does not make sense to add it. We will leave these questions for our future research topics.

Comment 2: The senior author is an expert not only for the basic science but for clinical patient treatment as well. The manuscript will markedly enhance its impact, if the authors can provide more information regarding the mechanisms of therapies, and potential new therapies against hTTP and/or iTTP. Is it possible to develop N-acetylcysteine (J Clin Invest. 2011 Feb;121(2):593-603.), anfibatide (Blood Adv. 2016 Nov 29;1(1):75-83; Sci Rep. 2021 Jun 3;11(1):11663; Thromb Haemost. 2014
Feb;111(2):279-89.) as useful therapeutic agents to control this life-threatening disease? The title of the manuscript may be modified if the authors can provide more information for the readers.

Reply 2: The pathogenetic mechanisms and novel therapeutics are discussed in a different article in this special series. These are all excellent questions. So we will not discuss this aspect in this article focusing on animal models.